REMARKS

Upon entry of the instant amendment, claims 1-13, 15-23, and 25-32 constitute the pending claims in the present application, and claims 1, 11, 13, 15-23, and 28-32 are currently under consideration. Applicants will cancel non-elected claims upon the indication of allowable subject matter. Applicants have also added new claims 30-32 to clarify the subject matter claimed. Support can be found throughout the specification, including the originally filed claims.

Applicants note that the amendment filed on August 20, 2002 has been entered in full, and the Examiner has acknowledged that priority under 35 U.S.C. 119(e) has been met.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim rejections under 35 USC §112, first paragraph

Claims 28 and 29 are rejected under 35 U.S.C. 112, first paragraph as being non-enabling. Specifically, the Office Action maintains that the instant specification provides no *in vivo – in vitro* correlation for the claimed pharmaceutical preparation, since the described *in vitro* effect of survival/outgrowth in peripheral ganglia does not correlate with a pharmaceutical having the activity of promoting survival, growth or inhibition of death or degeneration of any type of mammalian neural cell *in vivo*.

Pursuant to MPEP 2164.02:

> "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. ... In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34

> USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
>
> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

Evidently, based on the above passage, either an *in vitro* or an *in vivo* model is sufficient to support the claimed methods, as long as there is correlation between the model and the claimed use. The Office Action seems to have misinterpreted the standard as requiring both *in vitro* and *in vivo* correlation, and requires Applicants to provide an *in vivo* model, even in the presence of a correlating *in vitro* model. This is clearly inconsistent with the Office policy and the MPEP guideline set forth above. If Applicants were required to provide both *in vitro* and *in vivo* data to claim a pharmaceutical, then *in vitro* data would be irrelevant, as such data alone would never satisfy the standard of the Examiner.

Applicants submit that using cultured neural cells *in vitro* is a proper model that correlates with *in vivo* administration of morphogens and neurotrophic factors. If the combination of a morphogen and a NGF or a GDNF neurotrophic factor is known to promote neural cell survival *in vitro*, as shown in Figure 1, a skilled artisan would reasonably expect, in the absence of evidence to the contrary, that the same combination would have the same effect on neural cell survival *in vivo*. In contrast, other than simply dismissing the *in vitro* experiments as not correlating with the *in vivo* use, the Office Action provides neither scientific reasoning nor cited references to buttress its argument, thus failing to meet the initial burden required by MPEP to support its argument of no correlation and non-enablement, or to rebut the presumption in favor of Applicants. If the Examiner is relying on personal knowledge, Applicants respectfully request that the Examiner provide an affidavit pursuant to 37 C.F.R. 1.104(d)(2).

The Office Action also asserts that claim 29 is not enabled for the property of inhibiting death or degeneration because the instant examples disclose an effect of enhanced process formation, which is different for inhibition of death or degeneration.

Applicants submit that the examples explicitly disclose an effect of inhibiting neuron death or degeneration in Figure 1 (the vertical axis is labeled as "Sympathetic neuron survival (%)." Thus, Figure 1 teaches that in the absence of NGF, only about 5% of the control cells will

survive after 2 days in culture (or, about 95% of the control cells die / degenerate). In contrast, addition of NT-3 and OP-1, or GDNF and OP-1 remarkably inhibited this cell death / degeneration. This effect is also disclosed on page 22, lines 26-28: "[a] statistical analysis also shows differences in survival to be significant (Figure 1) as compared with the control (BME, or Basal Medium, Eagle's)." (emphasis added) Thus claim 29 is properly supported by the disclosure of the instant specification.

Claims 1, 13, and 15-23 are rejected under 35 U.S.C. §112, first paragraph, as lacking written description for survival of "different types of neural cells," such as CNS neurons, since the instant specification specifically teaches the survival or outgrowth of PNS neurons. The Office Action cites Jackowski and asserts that CNS damages are different from PNS damages.

Jackowski is a review article relating to CNS regeneration, especially CNS axonal regrowth (see lines 4-6 of the abstract), not neural cell survival as claimed in the instant application. Throughout the article, Jackowski focuses on the axonal regrowth in injured CNS tissues. See, for example, page 304, left column: "[t]he growth cones that lead the regenerating axons, grow towards and into the Schwann cell columns..."; also page 307, right column: "[a]bility of CNS axons to penentrate PNS grafts but not readily be able to re-enter the CNS." A skilled artisan would readily understand that CNS axon regeneration is quite different from CNS neural cell survival or death inhibition. The former require active regrowth of the damaged axon, while the latter does not. In this regard, Jackowski is largely irrelevant to the claimed invention.

Applicants teach that morphogen combined with neurotrophic factor enhances PNS neuron survival. Jackowski notes that the difference between the regenerative capability of the CNS and the PNS neurons is not due to the character of the neurons *per se* (also see **Exhibit A** below), but rather to the environment in which they reside, especially the supporting glial cells surrounding these neurons (with CNS containing astrocytes, microglia, ependymal cells, and oligodendrocytes; while PNS containing satellite cells and Schwann cells). Thus, in the absence of evidence to the contrary, a skilled artisan would readily expect that the CNS neurons would behave similarly in terms of survival upon contacting the morphogen / neurotrophic factor, as the PNS neurons do. To support the view that CNS and PNS neurons are not intrinsically different, Applicants submit herewith **Exhibit A** (Le Roux *et al.*, *Experimental Neurology* 160: 151-163), which indicates that OP-1 can also stimulate dendritic outgrowth in CNS neuron.

Since the initial burden is on the Examiner to give reasons for the lack of enablement (MPEP 2164.02), and since the Office Action has not cited any reference which suggests that there would be a difference in survival between CNS and PNS neural cells, Applicants submit that the claimed invention is enabled to its full scope of neural cells, based on the totality of the evidence presented above.

The Office Action also states that only OP-1 and NT-3 or OP-1 and GDNF are shown to be able to promote survival, not any morphogen or GDNF or NGF neurotrophic factors.

The test for enablement is whether one of skill in the art could practice the claimed invention without undue experimentation (MPEP 2164.01, also see *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404, Fed. Cir. 1988). A limited amount of experimentation is permissible under 35 U.S.C. 112, first paragraph, to determine whether a particular variant is operable, and that "the standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." (MPEP 2164.08(b)).

To provide additional evidence that the claimed invention is enabled for the full scope of morphogens, Applicants hereby submit a reference by Guo *et al.* (*Neurosci. Lett.* **245**(3):131-4, April 10, 1998, submitted herein as **Exhibit B**), which was published before the filing of the instant application, and which demonstrates that other morphogens encompassed by the 60% identity / 70% homology" terminology also possess an OP-1-like activity. Specifically, Guo *et al.* show that other recited morphogens, including the *Drosophila* protein 60A, possess the same ability as that of OP-1 to induce dendritic outgrowth. Since the morphogens encompassed by the claims all rely on the a common set of morphogen receptors for signaling (see page 465 of Heldin *et al.* Nature 390: 465-471, **Exhibit C**), a skilled artisan would reasonably expect that evidence obtained from one specific biological function (such as dendritic growth) can be used to support a different biological function. This is especially so in the instant case, where both biological functions are related to effects of morphogens in neuronal tissues. In other words, Guo demonstrates that a skilled artisan can successfully practice the claimed invention using all recited morphogens commensurate to the full scope of the claims, without resorting to any knowledge other than that already disclosed in the specification.

Especially worth mentioning is Table 1 of Guo, which indicates that BMP-3 "produced a slight but statistically significant increase in dendritic growth," (page 133, right column, lines 11-12 of Guo). Thus even if BMP-3 may not be the best available morphogens for practicing the claimed invention, if it can be used to practice the claimed invention, no matter how inefficient in achieving its intended effect, it is still enabled. Since seven-Cys skeleton sequence of BMP-3 is just about 40-50% identical to other morphogens described in the specification (see **Exhibit D**), these other claimed morphogens that exhibit greater sequence identity with OP-1 (than BMP-3), including but not limited to OP-2, BMP-5, BMP-6, BMP-2, BMP-4, Dpp may be reasonably expected to exhibit at least as much, if not more, OP-1-like activity in the claimed invention. In fact, Guo demonstrates that the *Drosophila* protein 60A (about 69% identical to human OP-1 in the highly conserved C-terminal Cys skeleton sequences, see **Exhibit D**) is quite effective in stimulating dendritic growth of mammalian (rat) neurons. In view of these data, a skilled artisan would reasonably conclude that all sequences represented by the presently claimed morphogens are enabled to the full scope. Indeed, Applicants submit that the specification has enabled *beyond* the presently claimed morphogens.

Regarding the neurotrophic factors, only GDNF, BDNF, NT-3, NT-4, NT-5, and NT-6 are recited in the claims. Among them, GDNF and NT-3 have been shown in the instant application to promote survival either along or synergistically with OP-1. In addition, the instant specification teaches: a) that all these neurotrophic factors share significant sequence homology with one another, especially the conserved six cysteine domain found in all neurotrophin family proteins, and b) that BDNF (page 14, line7), NT-4 (page 15, lines 20-21), and NT-5 (page 16, lines 10-11) all promotes neural survival. Also, according to Gotz *et al.* (*Nature* **327**: 266-269, November 17, 1994; cited on page 16, line16 of the specification), "[r]ecombinant purified NT-6 has a spectrum of actions similar to NGF on chick sympathetic and sensory neurons," indicating that NT-6 is also enabled.

Accordingly, in Applicants' view, the scope of the present claims fully satisfies the enablement requirement of 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 USC §103(a)

Claims 1, 11, 13 and 15-23 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over the Lein *et al.* reference in view of the Durbec *et al.* reference. Specifically, the Office Action contends that Lein *et al.* discloses that OP-1 and NGF are cofactors that influence dendritic growth in sympathetic neurons (emphasis added). The Office Action acknowledges that Lein *et al.* is directed exclusively to NGF, and is silent on other neurotrophic factors, such as GDNF. The Office Action further states that Durbec *et al.* discloses GDNF as a ligand for the c-ret receptor Tyrosine kinase (RTK). Thus, the Office Action concludes that it would have been obvious for a skilled artisan to combine Lein and Durbec to reach the conclusion that GDNF can substitute NGF, or tacit suggestion of the Office Action, that OP-1 and GDNF can influence dendritic growth in sympathetic neurons. The Office Action also argues that the motivation to combine is because GDNF belongs to the TGF-beta superfamily, which is the same superfamily that includes OP-1. The Office Action further asserts that there would be reasonable expectation of success, since all three factors (NGF, GDNF and OP-1) have been shown to have a positive effect on growth, survival, and/or differentiation of neural cells.

Pursuant to MPEP 2142, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

The Office Action's argument that a skilled artisan would be motivated to substitute NGF with GDNF is logically unsupported. According to the reasoning of the Office Action, even if there is a motivation to combine Durbec and Lein, would a skilled artisan end up substituting OP-1 with GDNF, rather than substituting NGF with GDNF? Since page 11 of the previous Office Action (Paper No. 8) states that "[t]he person of ordinary skill in the art would have been motivated to make the modification because GDNF belongs to transforming growth factor β

superfamily which is the same superfamily as OP-1." Therefore, GDNF would be regarded as functionally equivalent to OP-1, since they all belong to the TGF-beta superfamily. Applicants do not see how this reasoning can lead to the conclusion that NGF can be substituted by GDNF.

In addition, Applicants submit that a skilled artisan would have no motivation to combine Lein and Durbec in the first place, for the reasons which follow.

First of all, Lein suggests that NGF is a cofactor for OP-1 in OP-1-induced dendritic growth. Durbec discloses that GDNF is the previously unidentified cognate ligand of the c-ret Receptor Tyrosine Kinase (RTK). The only connections between GDNF and NGF, as the Office Action sees, are a) that GDNF is essential for PNS development, b) that PNS neurons express high levels of the c-ret receptor for GDNF, and c) both GDNF and NGF (and OP-1) allegedly have positive effects on neural growth, survival and/or differentiation. Applicants submit that neither a) nor b) conveys to a skilled artisan that GDNF and NGF are related, structurally or functionally, in any way. As to c), the mere observation that two things both have the same effect does not necessarily mean that they can always substitute for each other. Especially in view of the teaching of Durbec that GDNF is remotely related to OP-1 (but not NGF), substituting NGF (rather than OP-1) with GDNF would seem to be counter-intuitive.

Secondly, GDNF is a different kind of neurotropic factor from the NGF family of neurotropic factors. According to the instant specification (see the paragraph bridging pages 12 and 13), the GDNF family of neurotropic factors belongs to the TGF-beta superfamily of cytokines, but not to the OP/BMP subfamily within the TGF-beta superfamily. Therefore, GDNF also contain a seven-cysteine C-terminal domain, a feature lacking in the NGF family of neurotropic factors. In contrast, the NGF family of neurotropic factors, including NGF, BDNF, NT-3, NT-4, NT-5, and NT-6, share the same structural feature of 6 cysteines (different from the six- or seven-cysteine C-terminal domain of TGF-beta superfamily proteins). For example, a multisequence alignment of GDNF with the NGF family of neurotrophins indicates that the overall sequence identity between GDNF and any of the neurotrophins is less than 15%, while the neurotrophins are at least more than 30% identical to one another (with the exception of NT-6 being in the range of more than 20%) (**Exhibit E**). Therefore, even assuming for the sake of argument that combining morphogens and the NGF family of neurotrophins promotes cell survival, it is not obvious to combine morphogens with GDNF.

Finally, Lein does not teach or suggest any effect of OP-1/NGF in promoting cell survival as recited in claim 1, or in inhibiting cell death as recited in claim 29. In fact, Lein *teaches away* from the claimed invention by stating in page 212, last paragraph that "OP-1 . . . promotes the extension of dendrites without affecting cell survival," (emphasis added) thus discouraging a skilled artisan from attempting to study the effects of OP-1 in promoting cell survival, or inhibiting cell death, let alone its synergistic effect with neurotropic factors in promoting cell survival.

In summary, a skilled artisan would not be motivated to combine Lein and Durbec in the first place. Even if for the sake of argument, a skilled artisan combines Lein and Durbec, the artisan would substitute OP-1 with GDNF, and would not arrive at the claimed invention of combining OP-1 with GDNF. Even if GDNF can substitute NGF, the combined teaching is that OP-1 and GDNF might influence dendritic growth in sympathetic neurons, which is not what is claimed (neural survival). It naturally follows that the skilled artisan would have no reasonable expectation of success.

The Office Action dated November 12, 2002 recites, without providing reasoning, the last paragraph of Durbec, and page 3, lines 5-10, of the instant specification, to support the rejection under 35 U.S.C.103. The last paragraph of Durbec simply stresses the distant relationship between GDNF and the rest of the TGF-beta superfamily proteins, but does not in any way suggests that GDNF may be related to NGF or other NGF family of neurotrophins. Thus, it would not support a reason to substitute NGF with GDNF. The paragraph also speculates that other TGF-beta family members might bind RTKs, which is scientifically unproven at best, and clearly conflicts with the review article of Heldin *et al.* (supra, **Exhibit C**). Further, regardless of the truth of that statement, it also does not support a reason to substitute NGF with GDNF.

As to page 3, lines 5-10, of the instant specification, the Office Action contends that a skilled artisan would substitute NGF with GDNF in view of Lein and Durbec, simply because both GDNF and NGF are neurotrophic factors capable of promoting cell survival as described in the recited section of the instant specification. Assuming it is common knowledge that GDNF and NGF can both promote neural survival, and a skilled artisan knows: a) from Lein that OP-1 depends on NGF for dendritic outgrowth in rat sympathetic neurons, and b) from Durbec that

GDNF are distantly related to OP-1 since both belong to the TGF-beta superfamily, how then can the skilled artisan combine these sources of information, and reach the conclusion that GDNF can substitute NGF (rather than OP-1) to promote neural survival (rather than dendritic outgrowth)? In fact, a skilled artisan would have no motivation to combine these information in the first place, since these teachings do not appear to be relevant to one another. The same logic applies to the Office argument that GDNF can substitute NGF since they both signal through RTK. Nevertheless, to avoid confusion, Applicants have amended claims to separate the term "GDNF/NGF neurotrophic factor."

Based on the argument presented above, Applicants submit that none of the three requirements for establishing a *prima facie* case of obviousness is met. Reconsideration and withdrawal of the rejection under 35 U.S.C. 103 are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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Customer No: 28120
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050

Yu Lu, Ph.D.
Reg. No. 50,306